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Introduction

Neurofibromatosis 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All patients inevitably develop bilateral vestibular schwannomas that can lead to total deafness and death if left untreated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to vestibular schwannomas, and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of natural history of vestibular schwannomas, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study was to define the growth rate and clinical course of vestibular schwannomas in NF2-affected individuals. We accomplished this goal through the following steps:

1. Developed an international consortium of clinical centers and expertise in NF2.
2. Developed standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.
3. Analyzed standardized prospective neurophysiological/audiological results from NF2 patients.
4. Examined molecular, pathological, and clinical features that may predict tumor behavior.

Results of the study have led to a better understanding of the natural history and clinical course of vestibular schwannomas in NF2. The framework of clinical centers, data management, and scientific expertise established during this project is the core for future studies investigating other aspects of the natural history of NF2 and treatment trials in NF2.

Body

STATEMENT OF WORK

Natural History of Vestibular Schwannomas in Neurofibromatosis 2 (NF2)

Task 1. Development of an international consortium of clinical centers and expertise in NF2 and overall project activities.

a. Development of communication infrastructure for NF2 consortium members (month 1); Completed

A complete directory listing the site Co-Principal Investigators, Clinical Coordinators (CC), and other researchers involved in the NF2 study was created and distributed to study members. The directory, which presents phone numbers, fax numbers, addresses, and email addresses, allowed study members to communicate with each other when necessary. A List Server was established to facilitate rapid communication between the consortium sites through email.

b. Development of centralized data management system (months 1-3); Completed

A coordinated system for collecting and transmitting study data was established. A Procedure Manual documenting all study procedures was established and distributed to all Central Laboratory Centers and Patient Collection Centers (PCCs).

As detailed in the Procedure Manual, House Ear Institute (HEI) serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators initially faxed all completed data forms to HEI and later mailed all original forms at the end of the month. A Central Tracking System was established at HEI to track each subject and assure the consistent inflow of data from each site.

Files for each subject have been created and kept in a locked cabinet. A computerized database was created to house the study data and, as the forms were sent to HEI, the data were entered into the database.

c. Development of infrastructure within participating clinical centers to identify and recruit NF2 patients (months 1-3); Completed

A Clinical Coordinator (CC) was identified at each site, and the infrastructure for tracking patients has been established at each Patient Collection Center (PCC). The study protocol and the consent forms were submitted to local Institutional Review Boards at each site for approval. Each Patient Collection Center has an established NF2 database and/or has access to medical records with information on all the NF2 patients followed at their site. These were the basic sources for initial patient screening and identification. HEI submitted articles that were published in widely-read NF2 publications such as the *NNFF Newsletter* and the *NF2 Review*. A summary of the study was posted on several web sites including that of House Ear Institute, the NF2Crew, the National Neurofibromatosis Foundation, CenterWatch, and the National Cancer Institute. HEI received correspondence from interested NF2-affected individuals and from researchers around the world.

d. Train clinical centers' staff in study protocol (months 1-3); Completed

Clinical centers' staff was trained in study protocol at the initial Steering Committee Meeting on December 4, 1998. Grant protocol and procedure manual were distributed to each Co-PI and CC at each site. HEI maintained telephone discussions with the Clinical Coordinators to facilitate the study and the timely collection of data.

e. Identification and enrollment of 100 NF2 patients (months 1-3); Completed

Clinical Coordinators at each PCC screened their patient population and identified potential subjects for the NF2 Natural History study.

Table 1 below summarizes the current number of NF2 patients at each site who were enrolled.

Table 1: Patient Enrollment

Patient Collection Center	Location	Patients Enrolled
House Ear Institute:	Los Angeles, CA	42
MGH: MacCollin	Charlestown, MA	24
St. Mary's: Evans	Manchester, UK	16
Klinikum Nord Ochsensoll: Mautner	Hamburg, Germany	11
Mt. Sinai Medical Center: Rubenstein	New York, NY	2
Univ. Texas, Houston: Chang	Houston, TX	1
Royal Victorian Eye and Ear Hospital: Briggs	Melbourne, Australia	5
Ohio State Univ. Hospital: Welling	Columbus, OH	1
Nagoya University: Saito	Nagoya, Japan	4
Total Patients Enrolled		106

A major problem was patient accrual due to the unanticipated delay of Institutional Review Board (IRB) approval for all sites and delay in the Army approval of the Single Project Assurance (SPA) for the foreign sites. However, all PCCs were approved by local IRB and had Army approval. A second reason for enrollment problems was that Mt. Sinai had been expected to enroll upwards of 20 patients, but only two patients had been enrolled. To compensate for these problems, additional study sites were recruited and study inclusion criteria were expanded. As a result, study enrollment goals have been surpassed.

The allowance for inclusion of more than one NF2 patient from the same family was among the modifications made to the inclusion criteria to enhance patient enrollment. We do not believe that statistical independence of the study sample will be compromised for two reasons. First, very few patients (4 families w/ 9 NF2 patients) in this study have another family member who is also enrolled in this study. Secondly, while some correlation between NF2 genotype and phenotype (i.e., disease progression) exists, the genotype/phenotype correlation is not entirely clear. Further analysis is underway to examine this relationship. Therefore, we believe it highly unlikely that the addition of a small number of related patients will have any important effect on the observed results and conclusions.

See Table 2 below for dates of approval at each site.

Table 2: IRB approval dates for sites with full Army approval to enroll subjects.

Patient Collection Centers	IRB/Ethics Committee Approval	US Army Approval
House Ear Institute	February, 1998	December, 1998
MGH	March, 1999	June, 2000
Mt. Sinai	December, 1998	April, 2000
St. Mary's	February, 1999	March, 2000
Klinikum Nord Ochsenzoll	January, 1999	April, 2000
Royal Victorian Eye and Ear Hospital	March, 2000	October, 2000
Nagoya University	February, 2000	September, 2000
Ohio State University	April, 2000	January, 2001
University of Texas, Houston	April, 2000	September, 2000

From this section on, results will be discussed in terms of numbers of specific evaluations (MRI, audiology, etc.) received from subjects at the investigational sites.

f. Collection of baseline individual patient data (months 2-6); Completed

This section summarizes our collection of **baseline** data by specific type of evaluation.

MRI: One hundred patients (94% of enrolled patients) had their Baseline MRI exam. The remaining 6 exams were missed due to illness. Of the 100 patients who had Baseline MRI exams, WorldCare received the image data from 90 of these patients (85% of enrolled patients). Ten of the exams occurred, but were not received because no data was available to send to WorldCare. For example, a flood destroyed one of the patient's MRI films from the University of Texas site.

Audiology: Ninety-seven patients (92% of enrolled patients) had their Baseline Audiological exam, 9 exams were missed. Baseline Audiological data has been collected from 87 of these patients (82% of enrolled patients). For 10 exams that occurred, the data were not received at HEI. These 10 exams are from subjects at the St. Mary's site. St. Mary's did not have a full-time audiologist to conduct the exams and obtaining audiological exam results was difficult.

Clinical Exam: The primary reason for those patients missing a Baseline Clinical exam is that the decision to collect the Clinical Exam data was made after 37 enrolled patients had already passed their baseline exams. Therefore, there are 69 patients for whom we have had the opportunity to collect Baseline Clinical data. Sixty-nine patients (65% of enrolled patients) had their Baseline Clinical exam. Baseline Clinical data was collected from 67 of these patients (63% of enrolled patients).

All Baseline CRFs received were entered into the NF2 database.

Specifics of data collection are listed under tasks 2, 3, and 4.

g. Collection and computerization of yearly follow-up individual patient data (months 12-35); Completed

One-year follow-up (YR1), Two-year follow-up (YR2), and Interim data collection is summarized in a manner identical to that previously described in section 1f. Eighty-seven patients (82% of enrolled patients) had one-year follow-up. The remaining 19 patients did not have one-year follow-up due to their individual clinical course and/or the need for surgery. Two-year follow-up exams were conducted for 29 patients (27% of enrolled patients) due to varying enrollment times that do not allow two-year follow-up of all patients before the end of the study.

One-Year Follow-Up N=87

MRI: Seventy-seven patients (73% of enrolled patients) had their YR1 MRI exam. Ten exams are missing because no data was available to send to WorldCare. YR1 MRI exams were collected on 68 of these patients.

Audiology: Seventy-four patients (70% of enrolled patients) had their YR1 Audiological exam. YR1 Audiological data was collected from 68 of these patients. Exams from 6 patients were not received from St. Mary's due to problems at the St. Mary's site in obtaining a full-time audiologist to conduct the exams. The remaining 7 exams are missing due to patient illness.

Clinical Exam: Fifty-nine patients (56% of enrolled patients) had their YR1 Clinical exam. YR1 Clinical data was collected from all 59 of these patients.

Two-Year Follow-Up N=29

MRI: Twenty-eight patients (26% of enrolled) had their YR2 MRI exam. One exam is missing because no data was available to send to WorldCare. YR2 MRI was collected on 25 of these patients.

Audiology: Twenty-three patients (22% of enrolled patients) had their YR2 Audiological exam. Six exams were not received from St. Mary's due to problems at the St. Mary's site in obtaining a full-time audiologist. YR2 Audiological data was collected from all 23 of these patients.

Clinical Exam: Twenty-one patients (20% of enrolled patients) had their YR2 Clinical exam. YR2 Clinical data was collected from 20 of these patients.

Interim – These exams occurred between study evaluation dates for medical reasons. The data were collected for consistency with the study.

MRI: Seventy-four Interim MRI exams were conducted on 42 patients (40% of enrolled patients). Sixty of the Interim exams were received for 37 patients.

Audiology: Sixty-four Audiological exams were conducted on 37 patients (36% of enrolled patients). All 64 exams were received.

Clinical Exam: Twenty-seven Clinical exams were conducted on 20 patients (19% of enrolled patients). All 27 exams were received.

All YR1, YR2 and Interim CRFs received have been entered into the NF2 database.

h. Preparation of US Army grant for future clinical treatment outcome study (months 25-36); Completed

Exisulind, a drug developed by Cell Pathways, Inc. has been identified as a candidate treatment for NF2. This drug has been highly effective in inhibiting growth of other neoplasms that have many similarities to NF2, in addition to an excellent safety profile. Unpublished studies at HEI have found Exisulind to inhibit growth and increase apoptosis of NF2 cell cultures. Two grants were prepared and submitted for funding. The first was entitled "Drug Treatment for Neurofibromatosis Type II: Phase 2 Clinical Trial", submitted 9/5/00, and the second was entitled "Pilot Clinical Trial for Neurofibromatosis 2: Drug Treatment and Novel Surrogate Tumor Markers", submitted 7/31/01. However, grants submitted to the Department of Defense to conduct a Phase II treatment trial to treat NF2 patients with Exisulind were not selected for funding.

- i. Data editing, corrections, updates, and management (months 4-35); Completed**
Data editing, corrections, and updating were an ongoing process as data were submitted. The Clinical Coordinators reviewed the study data before forwarding it to the data management center at HEI. The HEI project manager and the statistician performed another review of the data. Clinical Coordinators were asked to re-submit any data that was problematic or to provide detailed information about any difficulties noticed in the data.
- j. Data analysis (months 6-12, 22-24, 34-36); Completed Retro MRI and Audiology**
Preliminary data analysis has been done on Retro MRI and Audiology exams. We have cleaned the data. This entailed checking all suspicious data values. Case Record Forms (CRFs), as well as the actual exam reports if necessary, were checked to ensure that the data were accurate. Additionally, each patient was reviewed individually to clearly identify the start point of the vestibular schwannoma as well as possible and the endpoint of any analysis. Each vestibular schwannoma (VS) was the unit of analysis with the start point the date at which the VS was first seen by MRI, and the endpoint being either the date of first VS treatment or date of last follow-up (whichever came first).
- k. Manuscript preparation (months 10-12, 22-24, 34-36); In Progress**
Manuscripts entitled "Short-term Audiometric Changes After Diagnosis in NF2," and "MRI Test-Retest of Vestibular Schwannomas in NF2" are currently being prepared.

Task 2. Standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.

- a. Development of standard operating procedure for digital analysis of MRIs (months 1-3); Completed**
A standard operating procedure manual (SOP) was completed for both the PCCs and the WorldCare Measurement Center. The WorldCare Patient Collection Center SOP was merged with the HEI procedure manual and was distributed to the CCs at each PCC.
- b. Set-up for communication of data to the statistical analysis and data management center (months 1-3); Completed**
There were two methods of data transfer to the Statistical Analysis and Data Management Center at HEI, optical disk and FTP. All measurement data recorded on the WorldCare Measurement Center MRI data forms were transferred via mail. All image data were transferred to HEI via CD-ROM. HEI was provided with a viewing system for these images complete with the measurement and viewing software Cheshire™.
- c. Preparation of facilities at WorldCare, Inc. (months 1-3); Completed**
A private suite for the NF2 Natural History Study was prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data were used for the collection and analysis of patient data. Also, the filing system, logbooks, and patient database were established to accept and track the workflow of patient data. An additional worksite was set up next to the initial worksite to facilitate the radiologist reading the scans. The additional worksite resulted in saving considerable time when measuring the tumors.
- d. Preparation of MRI facility to transmit data (months 1-3); Completed**
Each of the MRI facilities affiliated with the original Patient Collection Centers transmitted test data to WorldCare via optical disk or FTP. Certification of a MRI facility at the study sites is complete. As subjects were enrolled, the number of MRI facilities required to provide data expanded. As stated in the study protocol, each MRI facility had to become familiar with the scanning protocol,

agree to perform the scans as specified, and have their MRI equipment assessed for compatibility with WorldCare. Often times a follow-up MRI visit was done at a new MRI site that did not handle a patient's Baseline MRI scans. As a result, the process of certifying MRI facilities to send study data continued throughout the study.

e. Perform qualitative and quantitative analysis of MRIs (months 4-33); Completed

Retrospective films from 352 separate patient visits (from 105 enrolled patients) were collected and forwarded to WorldCare (WC). WC scanned these films in preparation for assessment and returned them to the study sites. The WC radiologist reviewed the scanned films and provided linear measurements of acoustic neuromas and/or meningiomas on Case Record Forms. In addition, the WC Radiologist noted whether or not the tumor had any cystic components, degenerative cysts, etc. These forms were sent to the Statistical Analysis and Data Management Center at HEI and entered into the study database.

As previously mentioned in section 1f, 90 patients had their baseline scans collected (i.e., WC received the image data from these MRI exams). Sixty-eight patients had their One-year Follow-up (YR1) exams sent to WC. Twenty-five patients had their Two-year Follow-up (YR2) exams sent to WC. Sixty patients had Interim prospective exams sent to WC.

f. Collection of MRI scan obtained prior to initiation of study (months 2-6); Completed

As stated above, MRI scans for 352 previous patient visits were obtained from the enrolled patients. The films were digitized and analyzed.

g. Collection of prospective MRI material (months 1-35); Completed

See Section 1f and 1g.

h. Transmitting volumetric data to the statistical analysis and data management center (months 4-35); Completed

Both measurement and image volumetric data were transmitted from WorldCare to the Statistical Analysis and Data Management Center at HEI. The image data were sent to HEI on CD-ROM and viewed with Cheshire™ software.

Task 3. Standardized prospective neurophysiological/audiological analysis of patients.

a. Training clinical centers on audiology protocol (months 1-3); Completed

The audiology protocol was distributed to the Patient Collection Centers and questions were directed to the Audiology Center Coordinator. Study audiologists were identified at each of the patient collection centers that agreed to conduct the examinations.

b. Development of communication pathways for audiology data management (months 1-3); Completed

The Statistical Analysis and Data Management/Coordinating Center at HEI managed the audiology data in the same manner as other study data. As outlined in the study Procedure Manual, completed forms were initially faxed to the HEI Project Manager and the original was mailed to HEI at the end of each month. Once the Project Manager received the completed *Audiology Data Form*, it was forwarded to the Audiology Center Coordinator at HEI to be reviewed. The data were then entered into the database.

c. Collection of audiometric testing performed prior to initiation of study (months 2-6); Completed

Retrospective audiological data were collected from 444 different patient visits (from 92 enrolled patients).

d. Collection of baseline audiometric data (months 2-6); Completed

See Section 1f.

e. Collection of follow-up yearly audiometric data (months 1-35); Completed

See Section 1g.

Task 4. Examination of molecular, pathological and clinical features which may predict tumor behavior.

a. Standardization of methods for pathological and molecular analysis (months 1-3); Completed

A standard protocol and report was established for review of pathological specimens (Dr. Louis) and for the molecular genetic analysis (Dr. MacCollin).

b. Establish method of data acquisition and transfer to the statistical analysis and data management center (months 1-3); Completed

As outlined in the NF2 Natural History Procedure Manual, data were acquired and recorded on the data forms which were then faxed and mailed to House Ear Institute.

c. Collection of pathological samples from tumors removed prior to initiation of study for analysis (months 4-9); Completed

Fifty-four patient's samples were sent for pathological analysis, including H&E slides, unstained slides and pathology reports. Forty-nine of these pathological analyses were completed. The other five analyses were not completed because they were sent to the contracted pathology analyst (Dr. Louis) after the contract deadline.

Genetic analysis was conducted on 99 patients, 68 of which were done by Dr. MacCollin's lab. Genetic information was received on 88 patients.

d. Collection of pathology samples from tumors removed during the course of the study (months 1-35); Completed

Overall, 16 vestibular schwannomas (VS) from 13 patients were removed during the course of the study. Eleven of these resected VS (from 8 patients) were collected by HEI. Thirteen patients had their second VS removed during the course of the study (first VS resected before entrance into the study).

Key Research Accomplishments

- Development of an international consortium of clinical centers and expertise in NF2.
- Establishment of standardized study protocol for multi-institutional, multi-national natural history study.
- Development of NF2 specific database which includes clinical, radiographical, audiometrical, pathology, and molecular biology/genetic information.
- Development of standard operating procedure for digital analysis of MRIs utilizing information from a variety of MRI machines from different manufacturers.
- Establishment of NF2 specific pathology specimen bank.
- Development of NF2 molecular biology database.

Reportable Outcomes

- Initial Steering Committee Meeting, December 4, 1998
- Progress Report, April, 1999, submitted to USAMRMC
- Progress Report, October, 1999, submitted to USAMRMC
- Progress Report, April, 2000, submitted to USAMRMC
- Steering Committee Meeting, June 4, 2000:
Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by Co-Principal Investigators.
- American Academy of Otolaryngology Head & Neck Surgery Meeting, September 24-27, 2000:
Considerations in the Development of the Neurofibromatosis 2 Natural History Consortium, paper submitted in February 2001
- Progress Report, October 2000, submitted to USAMRMC
- American Neurotology Society Meeting, May 12-13, 2001:
MRI Test-Retest of Vestibular Schwannomas in NF2, presentation and paper submitted in April 2001.
- American Neurotology Society Meeting, May 12-13, 2001:
Audiological Characteristics of Initial Presentation of NF2 Patients, presentation and paper to be submitted in April 2001.
- Society for Clinical Trials, May 20-23, 2001:
Poster presentation of "Design of a Multi-Center Natural History Study"
- Steering Committee Meeting, October 2001:
Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by Co-Principal Investigators.
- Presentations: "MRI Test-Retest of Vestibular Schwannomas in NF2", "Short-term Audiometric Changes After Diagnosis in NF2", "Volumetric Analysis of Vestibular Schwannomas in NF2".
- Final Report, March 2002, submitted to USAMRMC.

Conclusions

The infrastructure necessary for this project to be successful has been assembled. Subject enrollment had been difficult due to the delay in achieving Army approval of the informed consent forms for each institution and for Army approval of the Single Project Assurance for the foreign sites. Additionally, a Co-Principal Investigator left one of the core patient collection sites. Much effort was given to ensuring that the MRI facilities used by study participants were compatible with WorldCare's systems. The problem of slow enrollment was addressed through recruitment of additional sites, expansion of the inclusion criteria, and expanding the time for enrollment to occur. Seventy-nine subjects have both Baseline and One-year Follow-up exams completed. Thirty subjects have Baseline, One-year Follow-up and Two-year Follow-up exams completed. This is a unique and rich source of longitudinal data on NF2 patients.

References:

Publications in Review (Submitted)

1. "Considerations in the Development of Neurofibromatosis 2 Natural History Consortium"
2. "MRI Test-Retest of Vestibular Schwannomas in NF2"
3. "Short-term Audiometric Changes After Diagnosis in NF2"

Publications in Process

1. "Volumetric Analysis of Vestibular Schwannomas in NF2"
2. "Prospectively Collected ABR in NF2"